10-13-06

Express Mail No.: **EV531696457US**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Pettis *et al.*		Confirmation No.:	4336
Serial No.:	10/028,988	Group Art Unit:	3763
Filed:	December 28, 2001	Examiner:	Mendez, Manuel A.
For:	METHODS AND DEVICES FOR ADMINISTRATION OF SUBSTANCES INTO THE INTRADERMAL LAYER OF SKIN FOR SYSTEMIC ABSORPTION	Attorney Docket:	011219-022-999 (P4901 P5)

PETITION UNDER 37 C.F.R. § 1.181(a)
TO WITHDRAW HOLDING OF ABANDONMENT

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Pursuant to 37 C.F.R. § 1.181(a), Applicants hereby respectfully petition the United States Patent and Trademark Office ("Office") to withdraw the holding of abandonment of the above-identified application. A copy of the Notice of Abandonment dated August 16, 2006 ("Notice") is attached hereto as **Exhibit 1**.

The relevant facts are set forth below. On August 16, 2006 the Notice was mailed by the Office, and stated that the application was abandoned on the ground that no reply was received in response to Office letter mailed on February 9, 2006. However, Applicants respectfully submit an Amendment under 37 C.F.R. § 1.111, along with a Petition for Extension of Time under 37 C.F.R. § 1.136(a) and a Supplemental Declaration of Ronald J. Pettis under 37 C.F.R. § 1.132 with Exhibit A were filed with the Office on August 9, 2006.

In support of this Petition, Applicants submit herewith true copies of the following documents which were filed on August 9, 2006:

1. an Amendment under 37 C.F.R. § 1.111 (**Exhibit 2**);

2. a Petition for Extension of Time under 37 C.F.R. § 1.136(a) (**Exhibit 3**);

3. a Supplemental Declaration of Ronald J. Pettis under 37 C.F.R. § 1.132 with Exhibit A (**Exhibit 4**); and

4. a return receipt postcard bearing a date stamp of August 9, 2006 by the Office which, pursuant to M.P.E.P. 503, itemized and identified each item being filed (**Exhibit 5**).

Furthermore, Applicants submit that the Office's own PAIR records as of at least October 4, 2006 provide further evidence that Applicants' response of August 9, 2006 was timely filed and was received by the Office. A printout of the Document Description of the Imaged File Wrapper on October 4, 2006 shows an Amendment, Affidavit, and Extension of Time request designated with a mail room date of August 9, 2006 (**Exhibit 6**). Printouts downloaded from PAIR indicate that the first page of each of the items of the Response bears a date stamp of August 9, 2006 from the Office (**Exhibit 7**).

Accordingly, for the reasons set forth above, Applicants respectfully request that the Notice of Abandonment issued in connection with the subject application be withdrawn pursuant to the provisions of 37 C.F.R. § 1.181(a).

No fee is deemed necessary in connection with the filing of this Petition. However, should the Director determine that a fee is due, please charge the required amount to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

by: Jaqueline Benn
Reg No. 43,492

Date: October 11, 2006

Laura A. Coruzzi 30,742
Laura A. Coruzzi (Reg. No.)

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Enclosures

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,988 ✓	12/28/2001 ✓	Ronald J. Pettis	500752999021	4336

20583 7590 08/16/2006

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
MENDEZ, MANUEL A	

ART UNIT	PAPER NUMBER
3763	

DATE MAILED: 08/16/2006

011219-0022-999

Please find below and/or attached an Office communication concerning this application or proceeding.

Petition to Revive.
due 10-16-06.

Notice of Abandonment	Application No.	Applicant(s)	
	10/028,988	PETTIS ET AL.	
	Examiner	Art Unit	
	Manuel Mendez	3763	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *09 February 2006*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

Manuel Mendez
Primary Examiner
Art Unit: 3763

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

Express Mail No.: EV475142935US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: RONALD J. PETTIS, *et al.*

Confirmation No.: 4336

Serial No.: 10/028,988

Group Art Unit: 3763

Filed: December 28, 2001

Examiner: Mendez, Manuel A.

Attorney Docket No.: 11219-022-999
(500752 999 021; P-4901P5)

Date: August 9, 2006

For: METHODS AND DEVICES FOR ADMINISTRATION OF SUBSTANCES INTO THE INTRADERMAL LAYER OF SKIN FOR SYSTEMIC ABSORPTION

AMENDMENT UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action mailed February 9, 2006 (hereinafter "Office Action"), and pursuant to the provisions of Rule 111, please enter the amendments and consider the remarks below. Applicants submit herewith:

(1) a Petition for Extension of Time for three (3) months from May 9, 2006 up to and including August 9, 2006, with provision for payment of the required extension fee;

and

(2) A supplemental Declaration by Dr. Ronald J. Pettis under 37 C.F.R. §1.132.

The Commissioner is hereby authorized to charge any required fee(s) to Jones Day Deposit Account No. 503013.

Listing of Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

LISTING OF THE CLAIMS:

Please replace all prior claims in the application with the listing of claims below.

1. (Withdrawn) A method for directly delivering a substance into an intradermal space within a mammal, the method comprising bolus administration of said substance into the dermis, whereby the administered substance has at least one improved pharmacokinetic parameter relative to the same pharmacokinetic parameter produced upon administration of the same substance subcutaneously.

2. (Withdrawn) The method of claim 1 wherein the administering is through at least one small gauge hollow needle.

3. (Withdrawn) The method of claim 1 wherein the needle has an outlet with an exposed height between 0 and 1 mm.

4. (Withdrawn) The method of claim 1 wherein administering comprises inserting the needle to a depth which delivers the substance at least about 0.3 mm below the surface to no more than about 2 mm below the surface.

5. (Withdrawn) The method of claim 4 wherein administering comprises inserting the needle into the skin to a depth of at least about 0.3 mm and no more than about 2 mm.

6. (Withdrawn) The method of claim 1 wherein the improved pharmacokinetics is a decrease in T_{max}.

7. (Withdrawn) The method of claim 1 wherein the improved pharmacokinetics is an increase in C_{max}.

8. (Withdrawn) The method of claim 1 wherein the improved pharmacokinetics is a decrease in T_{lag}.

9. (Withdrawn) The method of claim 1 wherein the improved pharmacokinetics is an enhanced absorption rate.

10. (Withdrawn) The method of claim 1 wherein the substance is administered over a time period of not more than ten minutes.

11. (Withdrawn) The method of claim 1 wherein the substance is administered at a rate between 1 nl/min. and 200 ml/min.

12. (Withdrawn) The method of claim 1 wherein said substance is a hormone.

13. (Withdrawn) The method of claim 12 wherein the hormone is a growth hormone.

14. (Withdrawn) The method of claim 13 wherein the growth hormone is human growth hormone.

15. (Withdrawn) The method of claim 1 wherein the substance has a molecular weight greater than 1000 daltons.

16. (Withdrawn) The method of claim 1 wherein said substance is hydrophobic.

17. (Withdrawn) The method of claim 1 wherein said substance is hydrophilic.

18. (Withdrawn) The method of claim 1 wherein the needle(s) are inserted substantially perpendicularly to the skin.

19. (Withdrawn) A method of administering a pharmaceutical substance comprising administering the substance intradermally through one or more microneedles having a length and outlet suitable for selectively delivering the substance into the dermis over a time period of not more than ten minutes to obtain absorption of the substance in the dermis thereby producing improved systemic pharmacokinetics compared to subcutaneous administration.

20. (Withdrawn) The method of claim 19 wherein the improved pharmacokinetics is decreased T_{max}.

21. (Withdrawn) The method of claim 19 wherein the improved pharmacokinetics is an increase in C_{max}.

22. (Withdrawn) The method of claim 19 wherein the improved pharmacokinetics is a decrease in T_{lag}.

23. (Withdrawn) The method of claim 19 wherein the improved pharmacokinetics is an enhanced absorption rate.

24. (Withdrawn) The method of claim 19 wherein the length of the microneedle is from about 0.3 mm to about 2.0 mm.

25. (Withdrawn) The method of claim 19 wherein the microneedle is a 30 to 50 gauge needle.

26. (Withdrawn) The method of claim 19 wherein the microneedle has an outlet of from 0 to 1 mm.

27. (Withdrawn) The method of claim 19 wherein the microneedle is configured in a delivery device which positions the microneedle substantially perpendicular to skin surface.

28. (Withdrawn) The method of claim 19 wherein the microneedle needle is contained in an array of microneedles.

29. (Withdrawn) The method of claim 28 wherein the array comprises 3 microneedles.

30. (Withdrawn) The method of claim 28 wherein the array comprises 6 microneedles.

31. (Currently Amended) A method for administering a macromolecular pharmaceutical substance to a patient, the method comprising delivering a bolus of the substance intradermally via a needle inserted into the patient's skin so that the needle penetrates the intradermal compartment wherein the needle's outlet depth and exposed height of the outlet are located within the intradermal compartment, wherein the outlet has an exposed height of about 0 to 1mm, so that the substance is delivered into the intradermal compartment and distributed systemically exhibiting [to achieve] a higher C_{max} and a shorter T_{max} of the substance, by comparison with subcutaneous administration of the substance at an identical dose and rate of delivery.

32. (Previously Presented) The method of claim 31 or 67 wherein delivering the substance intradermally comprises injecting the substance intradermally.

33. (Previously Presented) The method of claim 31 or 67 wherein the administering comprises infusing the substance over a period of from about 2 min to about 10 min.

34. (Previously Presented) The method of claim 31 or 67 wherein the administering comprises delivering a bolus of the substance over a period of less than 10 minutes.

35. (Canceled) The method of claim 31 wherein administering the substance intradermally comprises administering the substance through a needle having a length and outlet configuration which allows selective intradermal delivery of the substance.

36. (Previously Presented) The method of claim 73 wherein the needle has a length of from about 0.3 m to about 2.0 mm.

37. (Previously Presented) The method of claim 73 wherein the needle is a 30 to 50 gauge needle.

38. (Previously Presented) The method of claim 73 wherein the needle is configured in a delivery device which positions the needle substantially perpendicular to skin surface.

39. (Previously Presented) The method of claim 73 wherein the needle is in an array of microneedles.

40. (Previously Presented) The method of claim 39 wherein the array comprises 3 microneedles.

41. (Previously Presented) The method of claim 39 wherein the array comprises 6 microneedles.

42. (Previously Presented) The method of claim 31 or 67 wherein the substance is administered at a volume rate of from about 2 microliters per minute to about 200 millileters per minute.

43. (Previously Presented) The method of claim 42 wherein the substance is administered at a volume rate of from about 2 microliters per minute to about 10 milliliters per minute.

44. (Previously Presented) The method of claim 42 wherein the substance is administered at a volume rate of from about 10 microliters per minute to about 200 millileters per minute.

45. (Previously Presented) The method of claim 31 wherein the substance comprises a polysaccharide.

46. (Previously Presented) The method of claim 31 wherein the substance comprises heparin molecule or a fragment thereof having anticoagulant activity.

47. (Previously Presented) The method of claim 31 wherein the substance comprises Fragmin®.

48. (Previously Presented) The method of claim 31 wherein the substance comprises a protein.

49. (Previously Presented) The method of claim 31 wherein the protein comprises a human growth hormone.

50. (Previously Presented) The method of claim 31 wherein the substance comprises Genotropin®.

51. (Previously Presented) The method of claim 42 wherein the rate is constant, variable or combinations thereof.

52. (Previously Presented) The method of claim 31 wherein the substance comprises a pegylated protein.

53. (Withdrawn) A method for delivering a bioactive substance to a subject comprising: contacting the skin of the subject with a device having a dermal-access means for accurately targeting the dermal space of the subject with an efficacious amount of the bioactive substance and administering a bolus of the substance into the dermis, wherein the pharmacokinetics of the bioactive substance is improved relative to the pharmacokinetics of the substance when administered subcutaneously.

54. (Withdrawn) The method of claim 53 wherein the improved pharmacokinetics is a decrease in T_{max}.

55. (Withdrawn) The method of claim 53 wherein the improved pharmacokinetics comprises an increase in C_{max} of the substance compared to subcutaneous injection.

56. (Withdrawn) The method of claim 53 wherein the improved pharmacokinetics is a decrease in T_{lag}.

57. (Withdrawn) The method of claim 53 wherein the device has a fluid driving means including a syringe, infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, or Belleville spring.

58. (Withdrawn) The method of claim 53 wherein the dermal access means comprises one or more hollow microcannula having a length of from about 0.3 to about 2.0 mm.

59. (Withdrawn) The method of claim 53 wherein said dermal access means comprises one or more hollow microcannula having an outlet with an exposed height between 0 and 1 mm.

60. (Withdrawn) A method for delivering a bioactive substance to a subject comprising: contacting the skin of a subject with a device having a dermal-access means for accurately targeting the dermal space of the subject with an efficacious amount of the bioactive substance at a rate of 1nl/min. to 200 ml/min. and delivering the substance into the dermis over a time period of not more than ten minutes; wherein the rapid onset pharmacokinetics of the bioactive substance is substantially improved relative to subcutaneous injection.

61. (Withdrawn) The method of claim 60 wherein the pharmacokinetics is a decreased T_{max}.

62. (Withdrawn) The method of claim 60 wherein the pharmacokinetics is an increased C_{max}.

63. (Withdrawn) The method of claim 60 wherein the pharmacokinetics is a decreased T_{lag}.

64. (Withdrawn) The method of claim 60 wherein the pharmacokinetics is an enhanced absorption rate.

65. (Withdrawn) The method of claim 60 wherein the dermal access means has one or more hollow microcannula that inserts into the skin of said subject to a depth of from about 0.3 to about 2.0 mm.

66. (Withdrawn) The method of claim 60 wherein the dermal access means has one or more hollow microcannula having an outlet with an exposed height between 0 and 1 mm.

67. (Currently Amended) A method for administering a hydrophobic pharmaceutical substance to a patient, the method comprising delivering a bolus of the substance intradermally <u>via a needle inserted into the patient's skin so that the needle penetrates the intradermal compartment wherein the needle's outlet depth and exposed height of the outlet are located within the intradermal compartment, wherein the outlet has an exposed height of about 0 to 1mm, so that the substance is delivered into the intradermal compartment and distributed systemically exhibiting</u> [to achieve] a higher C_{max} and a shorter T_{max} of the substance, by comparison with subcutaneous administration of the substance at an identical dose and rate of delivery.

68. (Previously Presented) The method of claim 31, wherein the macromolecular pharmaceutical substance has a molecular weight of at least 1000 Da.

69. (Previously Presented) The method of claim 31, wherein the macromolecular pharmaceutical substance has a molecular weight of at least 2000 Da.

70. (Previously Presented) The method of claim 31, wherein the macromolecular pharmaceutical substance has a molecular weight of at least 4000 Da.

71. (Previously Presented) The method of claim 31, wherein the macromolecular pharmaceutical substance has a molecular weight of at least 10,000 Da.

72. (Previously Presented) The method of claim 31, wherein the macromolecular pharmaceutical substance has a molecular weight of greater than 10,000 Da.

73. (Previously Presented) The method of claim 31 or 67, wherein administering the substance comprises the step of inserting the needle into the subject's skin so that the needle penetrates the intradermal compartment, and the needle's outlet depth and exposed height of the outlet are located within the intradermal compartment.

REMARKS

After entry of this amendment, claims 31-34, 36-52, 67-73 will be pending in the application. Claims 31 and 67 have been amended to more particularly point out and distinctly claim that which Applicant regards as the invention. The amendments are fully supported by the specification as originally filed and, as such no new matter has been added. Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

THE CLAIMS ARE NOT ANTICIPATED

Claims 31 and 32 are rejected under 35 U.S.C. § 102(b) as anticipated by Gross *et al.* (U.S. Patent No. 5,848,991). The Examiner contends that Gross inherently anticipates the claimed invention. For reasons detailed below, these rejections are erroneous and should be withdrawn.

First, the Examiner continues to erroneously interpret Gross as disclosing the delivery of drugs to the intradermal compartment of a human subject's skin using a single needle with an outlet at a depth of 250 microns to 2 mm. There simply is no description in Gross of a single needle having an outlet at that depth, furthermore Gross is devoid of any teaching of the depth at which the outlet falls within the skin.

Second, the Examiner has erroneously concluded that practicing Gross would inherently result in a pharmacokinetic profile (PK) similar to subcutaneous injection, but with a higher C_{max} and AUC. The Examiner has ignored the evidence provided by way of the Pettis Declaration submitted with the previous Amendment, dated October 31, 2005. The Pettis Declaration provides that the mere injection of a drug into the intradermal compartment does *not inevitably* result in a higher Cmax and a shorted Tmax as required by the claims. The Examiner has taken the position that Applicant has not proven that following the teachings of Gross would not result in the claimed pK profile.

While there is absolutely no evidence that practicing Gross would inherently result in the claimed PK profile, assuming *arguendo* Gross were used to inject a drug into the intradermal space, an enhanced PK profile as compared to subcutaneous delivery would *not inevitably* result. Mere injection of a drug into the intradermal compartment does not inevitably result in an enhancement of any PK parameters, let alone a higher C_{max} and shorter T_{max} as compared to subcutaneous delivery. In this regard, the Examiner's attention is invited to the Supplemental Declaration by Dr. Ronald J. Pettis under 37 C.F.R. §1.132, submitted herein ("the Supplemental Pettis Declaration") which evidences that mere injection of a drug to the intradermal compartment does *not inevitably* result in an enhanced PK profile as compared to subcutaneous delivery. In the particular example reported in the Supplemental Declaration, the T_{max}, C_{max} and AUC attained via intradermal delivery of Almotriptan was not significantly different from the T_{max}, C_{max} and AUC attained via subcutaneous delivery (*see* Supplemental Pettis Decl., ¶ 8).

In order for a prior art reference to inherently anticipate the claimed invention, the method disclosed must *inevitably* result in the claimed invention, *i.e.*, the claimed PK profile must be achieved *each time and every time* the methods of Gross are practiced. *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323 (C.C.P.A. 1981); *Continental Can Co. USA Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991); *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 34 U.S.P.Q. 2d 1565 (Fed. Cir. 1995). In other words, in order to establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *See*, M.P.E.P. Sec. No. 2112, IV citing to *In re Robertson* , 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). In this instance, the extrinsic evidence (*i.e.*, the Supplemental Pettis Declaration.) makes clear that the claim limitation which requires an enhanced PK profile as compared to subcutaneous delivery is

not necessarily present in the Gross reference. As demonstrated by the Supplemental Pettis Declaration merely depositing a substance into the intradermal compartment will not inevitably result in a PK profile having a higher C_{max} and shorter $T_{max,}$ as required by the claims. (*See* Supplemental Pettis Decl., ¶8). Since Gross would not *inevitably* lead to the PK profile claimed, inherent anticipation cannot be found, and the rejection should be withdrawn.

No where in Gross is there any recognition that intradermal delivery of a substance via a properly configured needle and the application of appropriate pressure results in any enhancement of PK parameters as compared to subcutaneous delivery. Thus, even if in some instance of practicing Gross an enhanced PK profile as compared to subcutaneous delivery were to result, such a result would be an unrecognized accident. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *See,* MPEP Sec. No. 2112, IV citing to *In re Robertson* , 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). An accidental or unwitting duplication of an invention cannot constitute an anticipation. *In re Marshall*, 198 U.S.P.Q. 344.

There is no evidence on this record that practicing the methods of Gross would inherently result in delivering a drug having the PK profile claimed. Moreover, the evidence provided herewith shows that the claimed PK profile would not inevitably result from practicing the prior art. In the event the Examiner disagrees, and to the extent that any rejection is based on facts within his personal knowledge, applicants request that the Examiner provide an affidavit pursuant to the provisions of 37 CFR § 1.104(d)(2).

1. THE CLAIMED INVENTION IS NOT OBVIOUS OVER GROSS IN VIEW OF PURI OR D'ANTONIO

Claims 33-52 are rejected under 35 U.S.C. §103(a) as obvious over Gross in view of Puri *et al.*, 2000, *Vaccine*, 18: 2600-12 ("Puri"), or U.S. Patent No. 6,056,716 to D'Antonio

("D'Antonio") and in further view of US Patent No. 3,814,097 to Ganderton *et al.* ("Ganderton"), and Autret et al., 1991, Therapie; 46:5-8 ("Autret").

The Examiner contends that to the extent Gross does not inherently achieve the claimed pharmacokinetic profile -- this missing element is supplied by Puri or D'Antonio. The obviousness rejection is based on the mistaken assertion that "Puri and D'Antonio disclose that intradermal injections give much greater C_{max} values than subcutaneous" (Office Action, p.4). The premise for this rejection is incorrect, and the rejection should be withdrawn.

The claimed methods relate to the delivery of a macromolecular or hydrophobic drug via bolus administration to the intradermal compartment via a needle with an outlet depth configured to achieve delivery of that substance in the intradermal compartment and with pharmacokinetic parameters similar to, but enhanced over subcutaneous delivery. There is nothing in the references combined to suggest the use of a needle with an outlet depth as specified by the claims, nor is there anything in the combination of references cited to suggest the use of a bolus delivery to achieve the enhanced PK parameters as claimed. In order to establish a *prima facie* case of obviousness, three criteria need be met: (1) there must be a suggestion or motivation to modify the reference or combine the teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations. *See*, the M.P.E.P. at Sect. 2143. In this instance, the *prima facie* case has not been made. First, for the reasons detailed below, the Examiner is inappropriately combining drug delivery and vaccine delivery art. One skilled in the art of drug delivery would not be motivated to attribute the teachings of vaccine art to drug delivery. Second, there is nothing in the art to suggest that the use of bolus delivery to the intradermal compartment will result in an enhanced PK profile as claimed. Third, the combination of

references cited fails to recite each of the claim limitations cited, *e.g.*, the use of a needle with an outlet depth as specified by the claims.

Puri, which deals with vaccine delivery (not drugs) is concerned with the body's immune response to the vaccine -- in other words, how much antibody the body makes in response to vaccination -- not systemic distribution profiles, and certainly not C_{max} levels of the administered vaccine. To illustrate the point, at pp. 2609 - 2610, Puri describes an enhanced *immune response* -- as measured by a higher antibody response -- not an enhanced C_{max} and AUC of the vaccine substance as the Examiner contends.

D'Antonio relates to jet injection of vaccines and other substances -- not the intradermal bolus delivery of macromolecular or hydrophobic drugs as claimed. Notably, at col. 29, line 3, D'Antonio expressly states that the entire discussion (of the D'Antonio patent) focused on *intramuscular injection.* The remainder of that paragraph discusses the possibility of administering vaccines -- *not drugs* -- into the dermis, so that less antigen could be used to generate "an increasingly rapid and effective pick-up by the immune system" (D'Antonio, col. 29, ll. 23-26).

Unlike drugs, the efficacy and potency of vaccines are not evaluated using PK studies. By contrast, the efficacy of vaccines is typically evaluated by measuring their ability to confer a protective immunity in the host. Methods for assaying potency of immunogenic compositions such as vaccines include serologic testing such as measurement of antibody titers induced against the particular antigen. For example in Puri, an ELISA assay was developed to quantify antibody levels (not the injected vaccines) in the sera of immunized mice. Similarly, D'Antonio makes reference, not to a PK profile, but rather to a more rapid and effective pickup by the immune system.

The Examiner has improperly attributed parameters and properties of the drug delivery art to the vaccine art. Pharmacokinetic studies are meaningless in the vaccine art as

practitioners in this field do not gauge the potency of the vaccine by its ability to be circulated systemically. In fact, as evidenced by the World Health Organization Guideline on Non-Clinical Evaluation of Vaccine, pharmacokinetic studies, *e.g.*, determining serum or tissue concentrations of the vaccine are normally not needed and in fact shed no light on the efficacy of the vaccine.

The Examiner relies on Ganderton for the purported teaching that multiple needle arrays result in facilitating the distribution of delivered drug to a patient. The Examiner posits that it would have been obvious to use the methods disclosed by Gross, Puri, and D'Antonio, to use the device of Ganderton.

The Examiner relies on Autret for the purported teaching that intradermal delivery of a hormone results in a pharmacokinetic profile similar to subcutaneous delivery. The Examiner posits that it would have been obvious to modify the methods disclosed by Gross, Puri, and D'Antonio, with hormone delivery disclosed by Autret, to achieve similar pharmacokinetic profiles via intradermal and subcutaneous delivery. As already described, the combination of Gross, Puri, and D'Antonio fails to satisfy the legal standard for an obviousness rejection, and Autret fails to cure the deficiency of such a combination.

Autret does not describe an intradermal delivery system which is the subject matter of the instant invention. As set out in the specification as filed (*see* ¶ [0007] of the instant specification), although Autret alleges intradermal delivery of calcitonin, the length of the needle and the angle at which the needle was used for drug administration would have resulted in either subcutaneous delivery or, at best, delivery into the reticular dermis where the substance would either be slowly absorbed or diffuse into the subcutaneous region, which would be the functional equivalent of subcutaneous administration and absorption. Thus, the method for hormone delivery taught in Autret results in subcutaneous delivery of the substance, which explains the similar pharmacokinetic profile between subcutaneous

administration and reported intradermal delivery, as opposed to the improved pharmacokinetic parameters required by the claimed invention.

Thus, skilled artisans concerned with drug administration via an intradermal delivery system, would not apply or combine the disclosure in Puri/D'Antonio and Ganderton and Autret with those in Gross. Moreover, the references must be viewed without the benefit of hindsight vision afforded by Applicants' claimed invention. *M.P.E.P. § 2141.* Absent a suggestion for the teaching that PK parameters can be altered and enhanced by intradermal injection relative to subcutaneous injection, the rejection cannot stand. Thus the rejections of claims 33-52 under 35 U.S.C. §103(a) should be withdrawn.

2. CONCLUSION

The Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted, by Jacqueline Benn
Reg No. 43,492

Date: August 9, 2006

Laura A. Coruzzi 30,742
Laura A. Coruzzi (Reg. No.)

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Express Mail No. EV475142935US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	RONALD J. PETTIS, et al.	Confirmation No.:	4336
Serial No.:	10/028,988	Art Unit:	3763
Filed:	December 28, 2001	Examiner:	Mendez, Manuel A.
For:	METHODS AND DEVICES FOR ADMINISTRATION OF SUBSTANCES INTO THE INTRADERMAL LAYER OF SKIN FOR SYSTEMIC ABSORPTION	Attorney Docket No:	11219-022-999 (500752-999021; P-4901P5)

PETITION FOR EXTENSION OF TIME UNDER 37 CFR § 1.136(a)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

It is respectfully requested that the time for response to the Office Action dated February 9, 2006 be extended for a period of 3 month(s) from May 9, 2006 to and including August 9, 2006.

The fee for this extension is estimated to be $1,020.00. Please charge the required fee to Jones Day Deposit Account No. 50-3013. A copy of this sheet is enclosed.

Respectfully submitted, by: Jacqueline Benn
Reg No. 43,492

Date: August 9, 2006

Laura A. Coruzzi 30,742
Laura A. Coruzzi (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017
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Express Mail No.: EV475142935US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: RONALD J. PETTIS, et al.	Confirmation No.: 4336
Serial No.:10/028,988	Art Unit: 3763
Filed: December 28, 2001	Examiner: Manuel A. Mendez
For: INTRADERMAL DELIVERY OF SUBSTANCES	Attorney Docket No.: 11219-022-999 (500752-999021; P-4901P5)

SUPPLEMENTAL DECLARATION OF DR. RONALD J. PETTIS UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, DR. RONALD J. PETTIS, do hereby declare and state:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-identified patent application (herein referred to as the '988 application).

2. I am currently a Senior Scientist, at Becton, Dickinson and Company, Inc. which is the assignee of the '988 application.

3. My academic background, technical experience and list of publications are set forth in my *curriculum vitae*, attached hereto as Exhibit A.

4. I have been asked to comment on whether intradermal delivery as practiced in accordance with the methods of the invention would always necessarily result in a higher AUC, C_{max} and/or a shorter T_{max} as compared to subcutaneous delivery.

5. As already described in the Declaration I submitted in connection with U.S. Application Serial No. 09/606,909 on January 6, 2005 ("the January Declaration"), my co-inventors and I developed an intradermal (ID) drug delivery system that results in an

improved pharmacokinetic profile similar to that observed with subcutaneous (SC) delivery, but with enhanced pharmacokinetic parameters. The improved pharmacokinetic profile can be manifested in two or more of the traditionally measured parameters, *e.g.*, faster T_{max} (the time required for the drug to reach a maximum serum concentration), increased C_{max} (the maximum (or peak) serum concentration of the drug reached within a given dose and route of administration), or increased AUC (the area under the serum concentration curve, which is a measure of bioavailability).

6. However, the injection of a drug to the intradermal comapartment does not inevitably result in an increased AUC, an increased C_{max} and/or a faster T_{max}. Various factors affect the resultant pharmacokinetic parameters, including the particular substance delivered, the rate of delivery used, and the mode of delivery. When a substance is delivered at a varied rate, pressure, volume or depth, a different pharmacokinetic profile may be obtained as evidenced by the data presented below. In particular, when Almotriptan was administered to the ID compartment as described in ¶¶ 7-9 below, the result was a pharmacokinetic profile nearly identical to SC delivery.

7. In the '988 application, Axert®, Almotriptan malate ("Almotriptan"), was delivered in a Yucatan mini pig model using a microneedle device (see Example XII of the '988 application). The microneedle had a total exposed length of 1 mm, designed such that the penetration of the needle outlet was limited to 1 mm. The Almotriptan delivery was controlled using a syringe pump (Harvard PHD 2000, Harvard Apparatus, Holliston, MA) wherein the rate of delivery was 45 μL/min and 180 μL/min. The delivery duration was 2-2.5 minutes. The pharmacokinetic parameters of intradermal and subcutaneous delivery of Almotriptan are summarized in Table 3 of the '988 application and reproduced below, in part, for convenience.

PK parameters	SC	ID
C_{max}(ng/mL)	61±19.4	63.6 (26.1)
T_{max}(h)	0.13 (0.05)	0.14 (0.008)
AUC	55.9 (6.04)	53.3 (15.7)

Table 3: Almotriptan PK Parameters Following SC and ID Administration

8. It is clear from an inspection of Table 3 that the pharmacokinetic profile and pharmacokinetic parameters of Almotriptan delivered to the intradermal space are similar to SC delivery, but not necessarily enhanced. Indeed, the AUC, C_{max} and T_{max} resulting from intradermal delivery as set out above closely resemble those resulting from SC delivery. This example thus unequivocally demonstrates that injection of a drug to the ID compartment does not inevitably result in enhanced pharmacokinetic parameters as compared to subcutaneous delivery.

9. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 19 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: August 9, 2006

/Ronald J. Pettis/

RONALD J. PETTIS

Exhibit A

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Ronald J. Pettis, Ph.D.	Sr. Scientist; Manager Therapeutic Drug Delivery
eRA COMMONS USER NAME	BD Technologies, Research Triangle Park, NC

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Georgia Institute of Technology	B.S. *cum laude*	1986	Chemistry
University of North Carolina at Chapel Hill	M.S	1988	Chemistry
University of North Carolina at Chapel Hill	Ph.D.	1991	Chemistry

Positions and Employment

1991-1994- Research Fellow, School of Pharmacy, University of North Carolina, Chapel Hill, NC
1994-1996 Research Associate, School of Pharmacy, University of North Carolina, Chapel Hill, NC
1996-2001 Scientist, Therapeutic Drug Delivery, BD Technologies, RTP, NC
2001-present Sr. Scientist, Manager, Therapeutic Drug Delivery, BD Technologies, RTP, NC

Honors and Professional Memberships

1990-present Member, American Association of Pharmaceutical Sciences
2003-present Member, Controlled Release Society
2000-present Member, BD Technologies Institutional Animal Care and Use Committee
2001 Wesley J. Howe Award for Technology Innovation, corporate achievement award

Issued Patents

1. United States Patent 6,440,096 August 27, 2002, Microdevice and method of manufacturing a microdevice, AG Lastovich; JD Evans; RJ Pettis
2. United States Patent 6,595,947 July 22, 2003, Topical delivery of vaccines; JA Mikszta; JM Brittingham; J Alarcon; RJ Pettis; JP Dekker III
3. United States Patent 6,607,513 August 19, 2003, Device for withdrawing or administering a substance and method of manufacturing a device; J. Down; NG Harvey; FE Martin; RJ Pettis, AG Lastovich
4. United States Patent 6,656,147 December 2, 2003 Method and delivery device for the transdermal administration of a substance; M Gertsek; BM Wilkinson; RJ Pettis
5. United States Patent 6,689,100 February 10, 2004 Microdevice and method of delivering or withdrawing a substance through the skin of an animal; RI Connelly, RJ Pettis
6. United States Patent 6,722,364 April 20, 2004 Medicament inhalation delivery devices and methods for using the same; RI Robert; VJ Sullivan; CD Shermer; A Bhuta; RJ Pettis
7. United States Patent 6,808,506. October 26, 2004, Device and method for delivering or withdrawing a substance through the skin, AG Lastovich; JK Fentress; J Griggs; RJ Pettis; D Sutter; FE Martin; MI Haider
8. United States Patent 6,858,018 February 22, 2005, Iontophoretic devices, PG Green; RJ Pettis; MR Brosnan-Cook
9. United States Patent 7,040,316 May 9, 2006, Medicament inhalation delivery devices and methods for using the same; RI Connelly; VJ Sullivan; CD Shermer; A Bhuta; RJ Pettis
10. United States Patent 7,060,059 June 13, 2006, System and method for initiating and maintaining continuous, long-term control of a concentration of a substance in a patient using a feedback or model-

based controller coupled to a single-needle or multi-needle intradermal (ID) delivery device, S Keith; RS Parker; NG Harvey; RJ Pettis, JD DeNuzzio; G Vonk

11. United States Patent United States Patent 7,083,592, August 1, 2006, Device and method for delivering or withdrawing a substance through skin, AG Lastovich, JK Fentress, J Griggs, RJ Pettis, D Sutter, FE Martin, MI Haider,
12. 36 patents pending

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2. Pettis RJ, Hall I, Costa D, Hickey AJ. Aerosol delivery of muramyl dipeptide to rodent lungs. AAPS PharmSci. 2000;2(3):article 25
3. Mikszta JA, Alarcon JB, Brittingham JM, Sutter DE, Pettis RJ, Harvey NG. Improved genetic immunization via micromechanical disruption of skin-barrier function and targeted epidermal delivery. Nat Med. 2002 Apr;8(4):415-9.
4. Pettis RJ, Knowles MR, Olivier KN, Kazantseva M, Hickey AJ. Ionic interaction of amiloride and uridine 5'-triphosphate in nebulizer solutions. J Pharm. Sci. 2004 Sep;93(9):2399-406.
5. Pettis RJ, Microneedle based drug delivery: a promising minimally invasive method for parenteral administration, Drug Delivery Companies Report, Spring/Summer 2004
6. Mikszta J, Haider MI, Pettis RJ, Microneedles for Drug and Vaccine Delivery in Skin delivery systems : transdermals, dermatologicals, and cosmetic actives, 1st ed; JJ. Wille ed., 2006
7. Laurent PE, Pettis RJ, Easterbrook W, Berube J, Evaluating New Hypodermic and Intradermal injection Devices, Med. Dev. Technology Mar; 17 (2), 2006

Abstracts

1. Pettis, RJ, Middleton, BA, Cho, MJ (1994) Preformulation studies of UCN-01: Solubility and stability enhancement by polyvinylpyrrolidone binding, Pharm. Res., 11:S230.
2. Pettis, RJ, Becton, BA, Cho, MJ, Tabibi, E (1995) Preformulation studies of sarcosine-chloroethylnitrosourea (SarCNU), Proc. Am. Assoc. Canc. Res., 36:311.
3. Atkins, KM, Lalor, CL, Concessio, NM, Pettis, RJ, Hickey, AJ (1995) Aerodynamic size characterization, lung deposition and alveolar macrophage uptake of microparticulate suspension aerosols in guinea pigs, abstract, 17th Annual Undergraduate Research Seminar, West Virginia University.
4. Lalor, CJ, Atkins, KM, Concessio, NM, Pettis, RJ, Hickey, AJ (1996) Lung deposition and alveolar macrophage uptake of microparticulates from suspension aerosols in guinea pigs, abstract, Society of Toxicology 35th Annual Meeting, Anaheim, CA.
5. Pettis, RJ, Hickey, AJ (1996) Alveolar macrophage activation by muramyl dipeptide aerosols in guinea pigs: Effects on cellular morphology, poster, AAPS Southeast Regional Meeting, Research Triangle Park, NC.
6. Pettis, RJ, Hickey, AJ (1996) Effect of muramyl dipeptide aerosols on guinea pig alveolar macrophages, Pharm. Res., 13(9):S166.
7. Pettis, RJ, Knowles, MR, Olivier, KN, Hickey, AJ (1996) Ionic interaction of amiloride and uridine-5'-triphosphate (UTP) in solution, Pharm. Res., 13(9):S179.
8. Pettis, RJ, Sutter, D, Dekker, J, Bock, R (2000) Microfabricated microneedles for disruption of skin barrier function, poster, 2000 AAPS Annual Meeting and Exposition.
9. Mikszta, J, Alarcon, J, Brittingham, JM, Dekker, JP, Pettis, RJ, Harvey, N G Microdevice-Based Topical Delivery of DNA and Subunit Vaccines. AAPS PharmSci Vol. 2, No. 2, Abstract 2307 (2000)
10. Pettis, RJ, Haider, I, Mikszta, J, Alarcon, J, Brittingham, JM, Davison, N, Solbrig, C, Zahn, J (2001) Hollow microneedle drug delivery systems: Biomechanical characterization and vaccine delivery, AAPSPharmSci, Vol. 3, No. 3

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13. **Pettis, RJ**, Kaestner, S, Sutter, D, Fentress, J, Harvey, N (2003) Microneedle-Based Intradermal Delivery of Insulin to Diabetic Swine: A Novel Parenteral Administration Method with Unique PK/PD Outcomes, podium, 2003 CRS Annual Meeting, Honolulu, HA
14. **Pettis, RJ**, Kaestner, S, Sutter, D, Fentress, J, Harvey, N (2004) *Microneedle-Based Intradermal Delivery of Insulin Enables Unique PK/PD Outcomes*, 2004 AAPS Annual Meeting, Baltimore, MD
15. Jiang, G, **Pettis, RJ**, Kuo, S, Harvey, AJ, Eicher, K, Kaestner, SA, Mitchell, M, Hwang, R, Haider, MI, Sullivan, V Intradermal delivery of novel sildenafil formulations, 2004 AAPS Annual Meeting, Baltimore, MD
16. Harvey, AJ, Kaestner, SA, Sutter, DE, Fentress, JK, **Pettis, RJ** (2005) Microneedle based delivery of follicle stimulating hormone : comparative pharmacokinetics vs. standard IM Therapy, 2005 CRS Annual Meeting and Exposition, Miami, FL
17. **Pettis, RJ**, Nycz, C, Harvey AJ, Karl K, Dunn B, Ramadan, S, Foster P (2006) In Vivo Cellular MRI for Tracking the Growth and Fate of Melanoma Cells Transplanted into Lymph Nodes of Mice 2006 Society for Molecular Imaging Meeting, Kona, HI
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19. Nycz, CM, Brittingham, J, Vonk, G, Mikszta, J, **Pettis, RJ** Sentinel Lymph Node Mapping Using Near IR Fluorescence Imaging and a Novel Lymph-Specific Delivery System 2006 Society for Molecular Imaging Meeting, Kona, HI

Current or Completed Research Support

None

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02

Date Mailed 8/9/2006

Serial No. 10/028,988 Filed December 28, 2001

Inventor RONALD J. PETTIS, et al.

For METHODS AND DEVICES FOR ADMINISTRATION OF SUBSTANCES INTO THE INTRADERMAL LAYER OF SKIN FOR SYSTEMIC ABSORPTION

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☐ Assignment	☒ Petition to Extend Time
☐ Brief (in Triplicate)	☐ Petition Under 37 C.F.R.
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☐ w.refs. ☐ w/o refs.	☐ Status Letter
☐ Drawings, Formal	☐ Transmittal Letter
Sheets Figures	☐ Fee By Deposit Account 3013

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Other: Supplemental Declaration of Dr. Ronald J. Pettis Under 37 C.F.R. 1.132 (Exhibit A)

File no.: 11219-022-999 (500752-999021; P-4901P5) Sender: LAC/JZB/pb

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10/028,988 Methods and devices for administration of substances into the i systemic absorption

Application Data | Transaction History | Image File Wrapper | Continuity Data | Published Documents | Publication Dates | Address & Attorney/Agent

This application is officially maintained in electronic form. To View: Click the desired Do
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02-06-2003	Power to Make Copies and/or Inspect	1
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11-08-2002	Applicant Arguments/Remarks Made in an Amendment	2
09-04-2002	Change of Address	1
04-04-2002	Pre-Exam Formalities Notice	1
12-28-2001	Issue Information including classification, examiner, name, claim, renumbering, etc.	1
12-28-2001	Search information including classification, databases and other search related notes	1

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: RONALD J. PETTIS, *et al.*

Confirmation No.: 4336

Serial No.: 10/028,988

Group Art Unit: 3763

Filed: December 28, 2001

Examiner: Mendez, Manuel A.

Attorney Docket No.: 11219-022-999
(500752 999 021; P-4901P5)

Date: August 9, 2006

For: METHODS AND DEVICES FOR ADMINISTRATION OF SUBSTANCES INTO THE INTRADERMAL LAYER OF SKIN FOR SYSTEMIC ABSORPTION

AMENDMENT UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action mailed February 9, 2006 (hereinafter "Office Action"), and pursuant to the provisions of Rule 111, please enter the amendments and consider the remarks below. Applicants submit herewith:

(1) a Petition for Extension of Time for three (3) months from May 9, 2006 up to and including August 9, 2006, with provision for payment of the required extension fee;

and

(2) A supplemental Declaration by Dr. Ronald J. Pettis under 37 C.F.R. §1.132.

The Commissioner is hereby authorized to charge any required fee(s) to Jones Day Deposit Account No. 503013.

Listing of Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

LISTING OF THE CLAIMS:

Please replace all prior claims in the application with the listing of claims below.

1. (Withdrawn) A method for directly delivering a substance into an intradermal space within a mammal, the method comprising bolus administration of said substance into the dermis, whereby the administered substance has at least one improved pharmacokinetic parameter relative to the same pharmacokinetic parameter produced upon administration of the same substance subcutaneously.

2. (Withdrawn) The method of claim 1 wherein the administering is through at least one small gauge hollow needle.

3. (Withdrawn) The method of claim 1 wherein the needle has an outlet with an exposed height between 0 and 1 mm.

4. (Withdrawn) The method of claim 1 wherein administering comprises inserting the needle to a depth which delivers the substance at least about 0.3 mm below the surface to no more than about 2 mm below the surface.

5. (Withdrawn) The method of claim 4 wherein administering comprises inserting the needle into the skin to a depth of at least about 0.3 mm and no more than about 2 mm.

6. (Withdrawn) The method of claim 1 wherein the improved pharmacokinetics is a decrease in T_{max}.

7. (Withdrawn) The method of claim 1 wherein the improved pharmacokinetics is an increase in C_{max}.

8. (Withdrawn) The method of claim 1 wherein the improved pharmacokinetics is a decrease in T_{lag}.

9. (Withdrawn) The method of claim 1 wherein the improved pharmacokinetics is an enhanced absorption rate.

10. (Withdrawn) The method of claim 1 wherein the substance is administered over a time period of not more than ten minutes.

11. (Withdrawn) The method of claim 1 wherein the substance is administered at a rate between 1 nl/min. and 200 ml/min.

12. (Withdrawn) The method of claim 1 wherein said substance is a hormone.

13. (Withdrawn) The method of claim 12 wherein the hormone is a growth hormone.

14. (Withdrawn) The method of claim 13 wherein the growth hormone is human growth hormone.

15. (Withdrawn) The method of claim 1 wherein the substance has a molecular weight greater than 1000 daltons.

16. (Withdrawn) The method of claim 1 wherein said substance is hydrophobic.

17. (Withdrawn) The method of claim 1 wherein said substance is hydrophilic.

18. (Withdrawn) The method of claim 1 wherein the needle(s) are inserted substantially perpendicularly to the skin.

19. (Withdrawn) A method of administering a pharmaceutical substance comprising administering the substance intradermally through one or more microneedles having a length and outlet suitable for selectively delivering the substance into the dermis over a time period of not more than ten minutes to obtain absorption of the substance in the dermis thereby producing improved systemic pharmacokinetics compared to subcutaneous administration.

20. (Withdrawn) The method of claim 19 wherein the improved pharmacokinetics is decreased T_{max}.

21. (Withdrawn) The method of claim 19 wherein the improved pharmacokinetics is an increase in C_{max}.

22. (Withdrawn) The method of claim 19 wherein the improved pharmacokinetics is a decrease in T_{lag}.

23. (Withdrawn) The method of claim 19 wherein the improved pharmacokinetics is an enhanced absorption rate.

24. (Withdrawn) The method of claim 19 wherein the length of the microneedle is from about 0.3 mm to about 2.0 mm.

25. (Withdrawn) The method of claim 19 wherein the microneedle is a 30 to 50 gauge needle.

26. (Withdrawn) The method of claim 19 wherein the microneedle has an outlet of from 0 to 1 mm.

27. (Withdrawn) The method of claim 19 wherein the microneedle is configured in a delivery device which positions the microneedle substantially perpendicular to skin surface.

28. (Withdrawn) The method of claim 19 wherein the microneedle needle is contained in an array of microneedles.

29. (Withdrawn) The method of claim 28 wherein the array comprises 3 microneedles.

30. (Withdrawn) The method of claim 28 wherein the array comprises 6 microneedles.

31. (Currently Amended) A method for administering a macromolecular pharmaceutical substance to a patient, the method comprising delivering a bolus of the substance intradermally <u>via a needle inserted into the patient's skin so that the needle penetrates the intradermal compartment wherein the needle's outlet depth and exposed height of the outlet are located within the intradermal compartment, wherein the outlet has an exposed height of about 0 to 1mm, so that the substance is delivered into the intradermal compartment and distributed systemically exhibiting</u> [to achieve] a higher C_{max} and a shorter T_{max} of the substance, by comparison with subcutaneous administration of the substance at an identical dose and rate of delivery.

32. (Previously Presented) The method of claim 31 or 67 wherein delivering the substance intradermally comprises injecting the substance intradermally.

33. (Previously Presented) The method of claim 31 or 67 wherein the administering comprises infusing the substance over a period of from about 2 min to about 10 min.

34. (Previously Presented) The method of claim 31 or 67 wherein the administering comprises delivering a bolus of the substance over a period of less than 10 minutes.

35. (Canceled) The method of claim 31 wherein administering the substance intradermally comprises administering the substance through a needle having a length and outlet configuration which allows selective intradermal delivery of the substance.

36. (Previously Presented) The method of claim 73 wherein the needle has a length of from about 0.3 m to about 2.0 mm.

37. (Previously Presented) The method of claim 73 wherein the needle is a 30 to 50 gauge needle.

38. (Previously Presented) The method of claim 73 wherein the needle is configured in a delivery device which positions the needle substantially perpendicular to skin surface.

39. (Previously Presented) The method of claim 73 wherein the needle is in an array of microneedles.

40. (Previously Presented) The method of claim 39 wherein the array comprises 3 microneedles.

41. (Previously Presented) The method of claim 39 wherein the array comprises 6 microneedles.

42. (Previously Presented) The method of claim 31 or 67 wherein the substance is administered at a volume rate of from about 2 microliters per minute to about 200 millileters per minute.

43. (Previously Presented) The method of claim 42 wherein the substance is administered at a volume rate of from about 2 microliters per minute to about 10 milliliters per minute.

44. (Previously Presented) The method of claim 42 wherein the substance is administered at a volume rate of from about 10 microliters per minute to about 200 millileters per minute.

45. (Previously Presented) The method of claim 31 wherein the substance comprises a polysaccharide.

46. (Previously Presented) The method of claim 31 wherein the substance comprises heparin molecule or a fragment thereof having anticoagulant activity.

47. (Previously Presented) The method of claim 31 wherein the substance comprises Fragmin®.

48. (Previously Presented) The method of claim 31 wherein the substance comprises a protein.

49. (Previously Presented) The method of claim 31 wherein the protein comprises a human growth hormone.

50. (Previously Presented) The method of claim 31 wherein the substance comprises Genotropin®.

51. (Previously Presented) The method of claim 42 wherein the rate is constant, variable or combinations thereof.

52. (Previously Presented) The method of claim 31 wherein the substance comprises a pegylated protein.

53. (Withdrawn) A method for delivering a bioactive substance to a subject comprising: contacting the skin of the subject with a device having a dermal-access means for accurately targeting the dermal space of the subject with an efficacious amount of the bioactive substance and administering a bolus of the substance into the dermis, wherein the pharmacokinetics of the bioactive substance is improved relative to the pharmacokinetics of the substance when administered subcutaneously.

54. (Withdrawn) The method of claim 53 wherein the improved pharmacokinetics is a decrease in T_{max}.

55. (Withdrawn) The method of claim 53 wherein the improved pharmacokinetics comprises an increase in C_{max} of the substance compared to subcutaneous injection.

56. (Withdrawn) The method of claim 53 wherein the improved pharmacokinetics is a decrease in T_{lag}.

57. (Withdrawn) The method of claim 53 wherein the device has a fluid driving means including a syringe, infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, or Belleville spring.

58. (Withdrawn) The method of claim 53 wherein the dermal access means comprises one or more hollow microcannula having a length of from about 0.3 to about 2.0 mm.

59. (Withdrawn) The method of claim 53 wherein said dermal access means comprises one or more hollow microcannula having an outlet with an exposed height between 0 and 1 mm.

60. (Withdrawn) A method for delivering a bioactive substance to a subject comprising: contacting the skin of a subject with a device having a dermal-access means for accurately targeting the dermal space of the subject with an efficacious amount of the bioactive substance at a rate of 1nl/min. to 200 ml/min. and delivering the substance into the dermis over a time period of not more than ten minutes; wherein the rapid onset pharmacokinetics of the bioactive substance is substantially improved relative to subcutaneous injection.

61. (Withdrawn) The method of claim 60 wherein the pharmacokinetics is a decreased T_{max}.

62. (Withdrawn) The method of claim 60 wherein the pharmacokinetics is an increased C_{max}.

63. (Withdrawn) The method of claim 60 wherein the pharmacokinetics is a decreased T_{lag}.

64. (Withdrawn) The method of claim 60 wherein the pharmacokinetics is an enhanced absorption rate.

65. (Withdrawn) The method of claim 60 wherein the dermal access means has one or more hollow microcannula that inserts into the skin of said subject to a depth of from about 0.3 to about 2.0 mm.

66. (Withdrawn) The method of claim 60 wherein the dermal access means has one or more hollow microcannula having an outlet with an exposed height between 0 and 1 mm.

67. (Currently Amended) A method for administering a hydrophobic pharmaceutical substance to a patient, the method comprising delivering a bolus of the substance intradermally via a needle inserted into the patient's skin so that the needle penetrates the intradermal compartment wherein the needle's outlet depth and exposed height of the outlet are located within the intradermal compartment, wherein the outlet has an exposed height of about 0 to 1mm, so that the substance is delivered into the intradermal compartment and distributed systemically exhibiting [to achieve] a higher C_{max} and a shorter T_{max} of the substance, by comparison with subcutaneous administration of the substance at an identical dose and rate of delivery.

68. (Previously Presented) The method of claim 31, wherein the macromolecular pharmaceutical substance has a molecular weight of at least 1000 Da.

69. (Previously Presented) The method of claim 31, wherein the macromolecular pharmaceutical substance has a molecular weight of at least 2000 Da.

70. (Previously Presented) The method of claim 31, wherein the macromolecular pharmaceutical substance has a molecular weight of at least 4000 Da.

71. (Previously Presented) The method of claim 31, wherein the macromolecular pharmaceutical substance has a molecular weight of at least 10,000 Da.

72. (Previously Presented) The method of claim 31, wherein the macromolecular pharmaceutical substance has a molecular weight of greater than 10,000 Da.

73. (Previously Presented) The method of claim 31 or 67, wherein administering the substance comprises the step of inserting the needle into the subject's skin so that the needle penetrates the intradermal compartment, and the needle's outlet depth and exposed height of the outlet are located within the intradermal compartment.

REMARKS

After entry of this amendment, claims 31-34, 36-52, 67-73 will be pending in the application. Claims 31 and 67 have been amended to more particularly point out and distinctly claim that which Applicant regards as the invention. The amendments are fully supported by the specification as originally filed and, as such no new matter has been added. Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

THE CLAIMS ARE NOT ANTICIPATED

Claims 31 and 32 are rejected under 35 U.S.C. § 102(b) as anticipated by Gross *et al.* (U.S. Patent No. 5,848,991). The Examiner contends that Gross inherently anticipates the claimed invention. For reasons detailed below, these rejections are erroneous and should be withdrawn.

First, the Examiner continues to erroneously interpret Gross as disclosing the delivery of drugs to the intradermal compartment of a human subject's skin using a single needle with an outlet at a depth of 250 microns to 2 mm. There simply is no description in Gross of a single needle having an outlet at that depth, furthermore Gross is devoid of any teaching of the depth at which the outlet falls within the skin.

Second, the Examiner has erroneously concluded that practicing Gross would inherently result in a pharmacokinetic profile (PK) similar to subcutaneous injection, but with a higher C_{max} and AUC. The Examiner has ignored the evidence provided by way of the Pettis Declaration submitted with the previous Amendment, dated October 31, 2005. The Pettis Declaration provides that the mere injection of a drug into the intradermal compartment does *not inevitably* result in a higher Cmax and a shorted Tmax as required by the claims. The Examiner has taken the position that Applicant has not proven that following the teachings of Gross would not result in the claimed pK profile.

While there is absolutely no evidence that practicing Gross would inherently result in the claimed PK profile, assuming *arguendo* Gross were used to inject a drug into the intradermal space, an enhanced PK profile as compared to subcutaneous delivery would *not inevitably* result. Mere injection of a drug into the intradermal compartment does not inevitably result in an enhancement of any PK parameters, let alone a higher C_{max} and shorter T_{max} as compared to subcutaneous delivery. In this regard, the Examiner's attention is invited to the Supplemental Declaration by Dr. Ronald J. Pettis under 37 C.F.R. §1.132, submitted herein ("the Supplemental Pettis Declaration") which evidences that mere injection of a drug to the intradermal compartment does *not inevitably* result in an enhanced PK profile as compared to subcutaneous delivery. In the particular example reported in the Supplemental Declaration, the T_{max}, C_{max} and AUC attained via intradermal delivery of Almotriptan was not significantly different from the T_{max}, C_{max} and AUC attained via subcutaneous delivery (*see* Supplemental Pettis Decl., ¶ 8).

In order for a prior art reference to inherently anticipate the claimed invention, the method disclosed must *inevitably* result in the claimed invention, *i.e.*, the claimed PK profile must be achieved *each time and every time* the methods of Gross are practiced. *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323 (C.C.P.A. 1981); *Continental Can Co. USA Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991); *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 34 U.S.P.Q. 2d 1565 (Fed. Cir. 1995). In other words, in order to establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *See,* M.P.E.P. Sec. No. 2112, IV citing to *In re Robertson* , 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). In this instance, the extrinsic evidence (*i.e.*, the Supplemental Pettis Declaration.) makes clear that the claim limitation which requires an enhanced PK profile as compared to subcutaneous delivery is

not necessarily present in the Gross reference. As demonstrated by the Supplemental Pettis Declaration merely depositing a substance into the intradermal compartment will not inevitably result in a PK profile having a higher C_{max} and shorter T_{max}, as required by the claims. (*See* Supplemental Pettis Decl., ¶8). Since Gross would not *inevitably* lead to the PK profile claimed, inherent anticipation cannot be found, and the rejection should be withdrawn.

No where in Gross is there any recognition that intradermal delivery of a substance via a properly configured needle and the application of appropriate pressure results in any enhancement of PK parameters as compared to subcutaneous delivery. Thus, even if in some instance of practicing Gross an enhanced PK profile as compared to subcutaneous delivery were to result, such a result would be an unrecognized accident. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *See,* MPEP Sec. No. 2112, IV citing to *In re Robertson* , 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). An accidental or unwitting duplication of an invention cannot constitute an anticipation. *In re Marshall*, 198 U.S.P.Q. 344.

There is no evidence on this record that practicing the methods of Gross would inherently result in delivering a drug having the PK profile claimed. Moreover, the evidence provided herewith shows that the claimed PK profile would not inevitably result from practicing the prior art. In the event the Examiner disagrees, and to the extent that any rejection is based on facts within his personal knowledge, applicants request that the Examiner provide an affidavit pursuant to the provisions of 37 CFR § 1.104(d)(2).

1. THE CLAIMED INVENTION IS NOT OBVIOUS OVER GROSS IN VIEW OF PURI OR D'ANTONIO

Claims 33-52 are rejected under 35 U.S.C. §103(a) as obvious over Gross in view of Puri *et al.*, 2000, *Vaccine*, 18: 2600-12 ("Puri"), or U.S. Patent No. 6,056,716 to D'Antonio

("D'Antonio") and in further view of US Patent No. 3,814,097 to Ganderton *et al.* ("Ganderton"), and Autret et al., 1991, Therapie; 46:5-8 ("Autret").

The Examiner contends that to the extent Gross does not inherently achieve the claimed pharmacokinetic profile -- this missing element is supplied by Puri or D'Antonio. The obviousness rejection is based on the mistaken assertion that "Puri and D'Antonio disclose that intradermal injections give much greater C_{max} values than subcutaneous" (Office Action, p.4). The premise for this rejection is incorrect, and the rejection should be withdrawn.

The claimed methods relate to the delivery of a macromolecular or hydrophobic drug via bolus administration to the intradermal compartment via a needle with an outlet depth configured to achieve delivery of that substance in the intradermal compartment and with pharmacokinetic parameters similar to, but enhanced over subcutaneous delivery. There is nothing in the references combined to suggest the use of a needle with an outlet depth as specified by the claims, nor is there anything in the combination of references cited to suggest the use of a bolus delivery to achieve the enhanced PK parameters as claimed. In order to establish a *prima facie* case of obviousness, three criteria need be met: (1) there must be a suggestion or motivation to modify the reference or combine the teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations. *See*, the M.P.E.P. at Sect. 2143. In this instance, the *prima facie* case has not been made. First, for the reasons detailed below, the Examiner is inappropriately combining drug delivery and vaccine delivery art. One skilled in the art of drug delivery would not be motivated to attribute the teachings of vaccine art to drug delivery. Second, there is nothing in the art to suggest that the use of bolus delivery to the intradermal compartment will result in an enhanced PK profile as claimed. Third, the combination of

references cited fails to recite each of the claim limitations cited, *e.g.*, the use of a needle with an outlet depth as specified by the claims.

Puri, which deals with vaccine delivery (not drugs) is concerned with the body's immune response to the vaccine -- in other words, how much antibody the body makes in response to vaccination -- not systemic distribution profiles, and certainly not C_{max} levels of the administered vaccine. To illustrate the point, at pp. 2609 - 2610, Puri describes an enhanced *immune response* -- as measured by a higher antibody response -- not an enhanced C_{max} and AUC of the vaccine substance as the Examiner contends.

D'Antonio relates to jet injection of vaccines and other substances -- not the intradermal bolus delivery of macromolecular or hydrophobic drugs as claimed. Notably, at col. 29, line 3, D'Antonio expressly states that the entire discussion (of the D'Antonio patent) focused on *intramuscular injection.* The remainder of that paragraph discusses the possibility of administering vaccines -- *not drugs* -- into the dermis, so that less antigen could be used to generate "an increasingly rapid and effective pick-up by the immune system" (D'Antonio, col. 29, ll. 23-26).

Unlike drugs, the efficacy and potency of vaccines are not evaluated using PK studies. By contrast, the efficacy of vaccines is typically evaluated by measuring their ability to confer a protective immunity in the host. Methods for assaying potency of immunogenic compositions such as vaccines include serologic testing such as measurement of antibody titers induced against the particular antigen. For example in Puri, an ELISA assay was developed to quantify antibody levels (not the injected vaccines) in the sera of immunized mice. Similarly, D'Antonio makes reference, not to a PK profile, but rather to a more rapid and effective pickup by the immune system.

The Examiner has improperly attributed parameters and properties of the drug delivery art to the vaccine art. Pharmacokinetic studies are meaningless in the vaccine art as

practitioners in this field do not gauge the potency of the vaccine by its ability to be circulated systemically. In fact, as evidenced by the World Health Organization Guideline on Non-Clinical Evaluation of Vaccine, pharmacokinetic studies, *e.g.*, determining serum or tissue concentrations of the vaccine are normally not needed and in fact shed no light on the efficacy of the vaccine.

The Examiner relies on Ganderton for the purported teaching that multiple needle arrays result in facilitating the distribution of delivered drug to a patient. The Examiner posits that it would have been obvious to use the methods disclosed by Gross, Puri, and D'Antonio, to use the device of Ganderton.

The Examiner relies on Autret for the purported teaching that intradermal delivery of a hormone results in a pharmacokinetic profile similar to subcutaneous delivery. The Examiner posits that it would have been obvious to modify the methods disclosed by Gross, Puri, and D'Antonio, with hormone delivery disclosed by Autret, to achieve similar pharmacokinetic profiles via intradermal and subcutaneous delivery. As already described, the combination of Gross, Puri, and D'Antonio fails to satisfy the legal standard for an obviousness rejection, and Autret fails to cure the deficiency of such a combination.

Autret does not describe an intradermal delivery system which is the subject matter of the instant invention. As set out in the specification as filed (*see* ¶ [0007] of the instant specification), although Autret alleges intradermal delivery of calcitonin, the length of the needle and the angle at which the needle was used for drug administration would have resulted in either subcutaneous delivery or, at best, delivery into the reticular dermis where the substance would either be slowly absorbed or diffuse into the subcutaneous region, which would be the functional equivalent of subcutaneous administration and absorption. Thus, the method for hormone delivery taught in Autret results in subcutaneous delivery of the substance, which explains the similar pharmacokinetic profile between subcutaneous

administration and reported intradermal delivery, as opposed to the improved pharmacokinetic parameters required by the claimed invention.

Thus, skilled artisans concerned with drug administration via an intradermal delivery system, would not apply or combine the disclosure in Puri/D'Antonio and Ganderton and Autret with those in Gross. Moreover, the references must be viewed without the benefit of hindsight vision afforded by Applicants' claimed invention. *M.P.E.P. § 2141.* Absent a suggestion for the teaching that PK parameters can be altered and enhanced by intradermal injection relative to subcutaneous injection, the rejection cannot stand. Thus the rejections of claims 33-52 under 35 U.S.C. §103(a) should be withdrawn.

2. CONCLUSION

The Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted, by Jacqueline Benn
Reg No. 43,492

Date: August 9, 2006

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: RONALD J. PETTIS, et al.	Confirmation No.: 4336
Serial No.:10/028,988	Art Unit: 3763
Filed: December 28, 2001	Examiner: Manuel A. Mendez
For: INTRADERMAL DELIVERY OF SUBSTANCES	Attorney Docket No.: 11219-022-999 (500752-999021; P-4901P5)

SUPPLEMENTAL DECLARATION OF DR. RONALD J. PETTIS UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, DR. RONALD J. PETTIS, do hereby declare and state:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-identified patent application (herein referred to as the '988 application).

2. I am currently a Senior Scientist, at Becton, Dickinson and Company, Inc. which is the assignee of the '988 application.

3. My academic background, technical experience and list of publications are set forth in my *curriculum vitae*, attached hereto as Exhibit A.

4. I have been asked to comment on whether intradermal delivery as practiced in accordance with the methods of the invention would always necessarily result in a higher AUC, C_{max} and/or a shorter T_{max} as compared to subcutaneous delivery.

5. As already described in the Declaration I submitted in connection with U.S. Application Serial No. 09/606,909 on January 6, 2005 ("the January Declaration"), my co-inventors and I developed an intradermal (ID) drug delivery system that results in an

improved pharmacokinetic profile similar to that observed with subcutaneous (SC) delivery, but with enhanced pharmacokinetic parameters. The improved pharmacokinetic profile can be manifested in two or more of the traditionally measured parameters, *e.g.*, faster T_{max} (the time required for the drug to reach a maximum serum concentration), increased C_{max} (the maximum (or peak) serum concentration of the drug reached within a given dose and route of administration), or increased AUC (the area under the serum concentration curve, which is a measure of bioavailability).

6. However, the injection of a drug to the intradermal comapartment does not inevitably result in an increased AUC, an increased C_{max} and/or a faster T_{max}. Various factors affect the resultant pharmacokinetic parameters, including the particular substance delivered, the rate of delivery used, and the mode of delivery. When a substance is delivered at a varied rate, pressure, volume or depth, a different pharmacokinetic profile may be obtained as evidenced by the data presented below. In particular, when Almotriptan was administered to the ID compartment as described in ¶¶ 7-9 below, the result was a pharmacokinetic profile nearly identical to SC delivery.

7. In the '988 application, Axert®, Almotriptan malate ("Almotriptan"), was delivered in a Yucatan mini pig model using a microneedle device (see Example XII of the '988 application). The microneedle had a total exposed length of 1 mm, designed such that the penetration of the needle outlet was limited to 1 mm. The Almotriptan delivery was controlled using a syringe pump (Harvard PHD 2000, Harvard Apparatus, Holliston, MA) wherein the rate of delivery was 45 µL/min and 180 µL/min. The delivery duration was 2-2.5 minutes. The pharmacokinetic parameters of intradermal and subcutaneous delivery of Almotriptan are summarized in Table 3 of the '988 application and reproduced below, in part, for convenience.

PK parameters	SC	ID
C_{max}(ng/mL)	61±19.4	63.6 (26.1)
T_{max}(h)	0.13 (0.05)	0.14 (0.008)
AUC	55.9 (6.04)	53.3 (15.7)

Table 3: Almotriptan PK Parameters Following SC and ID Administration

8. It is clear from an inspection of Table 3 that the pharmacokinetic profile and pharmacokinetic parameters of Almotriptan delivered to the intradermal space are similar to SC delivery, but not necessarily enhanced. Indeed, the AUC, C_{max} and T_{max} resulting from intradermal delivery as set out above closely resemble those resulting from SC delivery. This example thus unequivocally demonstrates that injection of a drug to the ID compartment does not inevitably result in enhanced pharmacokinetic parameters as compared to subcutaneous delivery.

9. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 19 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: August 9, 2006

/Ronald J. Pettis/

RONALD J. PETTIS

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
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NAME	POSITION TITLE
Ronald J. Pettis, Ph.D.	Sr. Scientist; Manager Therapeutic Drug Delivery,
eRA COMMONS USER NAME	BD Technologies, Research Triangle Park, NC

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Georgia Institute of Technology	B.S. *cum laude*	1986	Chemistry
University of North Carolina at Chapel Hill	M.S	1988	Chemistry
University of North Carolina at Chapel Hill	Ph.D.	1991	Chemistry

Positions and Employment

1991-1994- Research Fellow, School of Pharmacy, University of North Carolina, Chapel Hill, NC
1994-1998 Research Associate, School of Pharmacy, University of North Carolina, Chapel Hill, NC
1998-2001 Scientist, Therapeutic Drug Delivery, BD Technologies, RTP, NC
2001-present Sr. Scientist, Manager, Therapeutic Drug Delivery, BD Technologies, RTP, NC

Honors and Professional Memberships

1990-present Member, American Association of Pharmaceutical Sciences
2003-present Member, Controlled Release Society
2000-present Member, BD Technologies Institutional Animal Care and Use Committee
2001 Wesley J. Howe Award for Technology Innovation, corporate achievement award

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2. United States Patent 6,595,947 July 22, 2003, Topical delivery of vaccines; JA Mikszta; JM Brittingham; J Alarcon; RJ Pettis; JP Dekker III
3. United States Patent 6,607,513 August 19, 2003, Device for withdrawing or administering a substance and method of manufacturing a device; J. Down; NG Harvey; FE Martin; RJ Pettis, AG Lastovich
4. United States Patent 6,656,147 December 2, 2003 Method and delivery device for the transdermal administration of a substance; M Gertsek; BM Wilkinson; RJ Pettis
5. United States Patent 6,689,100 February 10, 2004 Microdevice and method of delivering or withdrawing a substance through the skin of an animal; RI Connelly, RJ Pettis
6. United States Patent 6,722,364 April 20, 2004 Medicament inhalation delivery devices and methods for using the same; RI Robert; VJ Sullivan; CD Shermer; A Bhuta; RJ Pettis
7. United States Patent 6,808,506. October 26, 2004, Device and method for delivering or withdrawing a substance through the skin, AG Lastovich; JK Fentress; J Griggs; RJ Pettis; D Sutter; FE Martin; MI Haider
8. United States Patent 6,858,018 February 22, 2005, Iontophoretic devices, PG Green; RJ Pettis; MR Brosnan-Cook
9. United States Patent 7,040,316 May 9, 2006, Medicament inhalation delivery devices and methods for using the same; RI Connelly; VJ Sullivan; CD Shermer; A Bhuta; RJ Pettis
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19. Nycz, CM, Brittingham, J, Vonk, G, Mikszta, J, **Pettis, RJ** Sentinel Lymph Node Mapping Using Near IR Fluorescence Imaging and a Novel Lymph-Specific Delivery System 2006 Society for Molecular Imaging Meeting, Kona, HI

Current or Completed Research Support

None

Express Mail No. EV475142935US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	RONALD J. PETTIS, et al.	Confirmation No.:	4336
Serial No.:	10/028,988	Art Unit:	3763
Filed:	December 28, 2001	Examiner:	Mendez, Manuel A.
For:	METHODS AND DEVICES FOR ADMINISTRATION OF SUBSTANCES INTO THE INTRADERMAL LAYER OF SKIN FOR SYSTEMIC ABSORPTION	Attorney Docket No:	11219-022-999 (500752-999021; P-4901P5)

PETITION FOR EXTENSION OF TIME UNDER 37 CFR § 1.136(a)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

It is respectfully requested that the time for response to the Office Action dated February 9, 2006 be extended for a period of 3 month(s) from May 9, 2006 to and including August 9, 2006.

The fee for this extension is estimated to be $1,020.00. Please charge the required fee to Jones Day Deposit Account No. 50-3013. A copy of this sheet is enclosed.

Respectfully submitted, by: Jacqueline Benn
Reg No. 43,492

Date: August 9, 2006

Laura A. Coruzzi 30,742
Laura A. Coruzzi (Reg. No.)

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